



# The efficacy of ginseng supplementation on plasma lipid concentration in adults: A systematic review and meta-analysis

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## ABSTRACT

**Objective:** We performed a meta-analysis to evaluate the efficacy of ginseng supplementation on plasma lipid concentration.

**Methods:** The search included PubMed, Scopus, ISI Web of Science, Cochrane library, and Google Scholar (up to April 2019) to identify randomized controlled trials (RCTs) investigating the effect of ginseng supplementation on serum lipid parameters. To estimate the overall summary effect, we used random-effects model.

**Results:** Twenty-seven studies comprising 35 treatment arms comprising 1245 participants fulfilled the inclusion criteria. The meta-analysis results showed that consumption of ginseng did not significantly change the concentrations of total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C). However, subgroup analyses showed a significant lowering effect in high dose ginseng supplementation on TC, LDL-C and TG. Also, the impact of ginseng on TC and TG was significant in long-term interventions.

**Conclusion:** Further RCTs with longer supplementation durations in subjects with dyslipidemia are necessitated for a more robust assessment of the lipid-modulating properties of this plant.

## 1. Introduction

Cardiovascular disease (CVD) is recognized as one of the leading causes of early mortality, accounting for more than 30% of total death globally.<sup>1</sup> In recent years, CVD prevalence has markedly increased in developing countries.<sup>2,3</sup> Dyslipidemia is one of the most important and modifiable CVD risk factors reported to be present in more than 90% of patients with coronary heart disease.<sup>4,5</sup> Dyslipidemia refers to a group of lipid abnormalities including elevated low-density lipoprotein-cholesterol (LDL-C), hypercholesterolemia, hypertriglyceridemia and low high-density lipoprotein-cholesterol (HDL-C).<sup>6</sup> Despite improvement in diagnosis and treatment approaches, management of dyslipidemia remains challenging. In this case, there has been growing interest in elucidating the efficacy of other treatments with fewer side-effects; among them, herbal medicine has received vast attention.<sup>7,8</sup>

Ginseng is an herb derived from several species of the genus *Panax*, which belongs indigenously to Asia and North America, and has been used in traditional medicine for several centuries for various diseases; with some previous studies reporting a wide range of biological activities of ginseng, including anti-inflammatory, antioxidant, anticancer, and anti-stress effects.<sup>9–12</sup> Thirteen distinct species of ginseng have been identified; the most popular and most studied species are American (*Panax quinquefolius* L) and Asian (*Panax ginseng*) ginseng.<sup>13</sup> Three types of ginseng are currently available: fresh, white and red ginseng. White ginseng is made from peeled and dried fresh ginseng, but red ginseng is made by steaming fresh ginseng.<sup>14,15</sup> Red ginseng reportedly possesses greater bioactivity than the unprocessed white ginseng roots.<sup>16</sup> Ginsenosides (triterpene b-glycosides) are the pharmacologically active components and are responsible for the biological functions in ginseng. More than 150 types of ginsenosides have been identified.<sup>17</sup>

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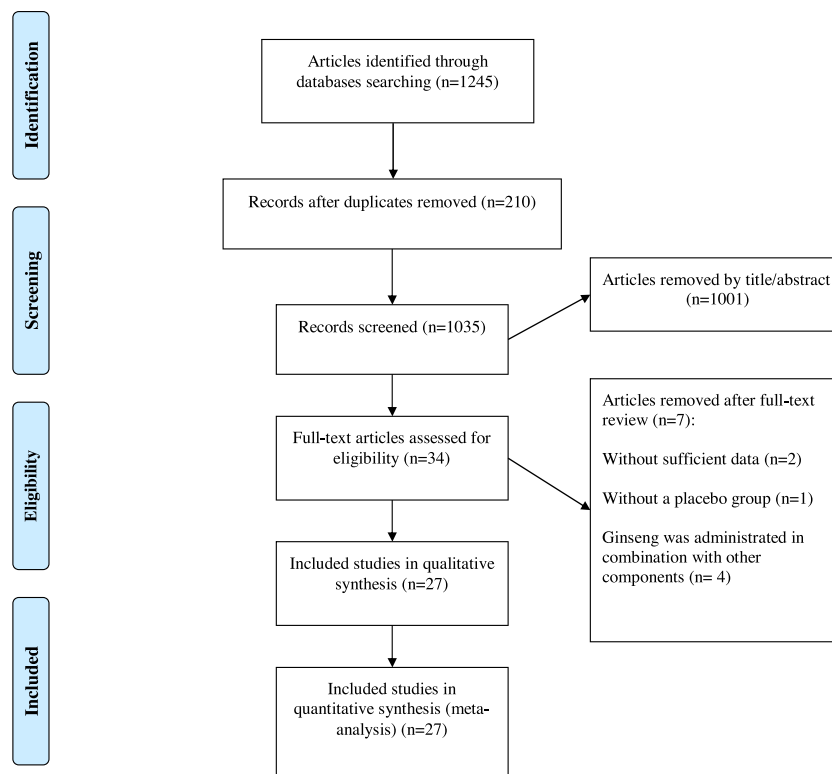


Fig. 1. PRISMA flow diagram of study selection process.

Major ones are Rb1, Rb2, Rc, Rd, Re, Rg1, and Rf, which account for more than 80% of the total ginsenosides in ginseng.<sup>10,18</sup> In the gastrointestinal tract, these ginsenosides are changed by gut microbiota, which improves their intestinal absorption, increases their bioactivity, and decreases the toxicity of the metabolites.<sup>19,20</sup>

Favorable effects of ginseng on improving lipid metabolism and blood lipids have been reported in several experimental studies.<sup>21–26</sup> Several mechanisms have been proposed to explain the antihyperlipidemic effects of ginseng in humans, such as anti-inflammatory and antioxidative properties, reducing hepatic cholesterol and TG levels by activation of AMP-activated protein kinase (AMPK).<sup>23,27,28</sup> Nevertheless, findings from human studies are inconsistent in this context. While some studies supported the beneficial effects of ginseng supplementation on blood lipid concentrations,<sup>29,30</sup> several clinical trials have failed to show a significant effect.<sup>17,20,31</sup> In addition, as far as we know, there is no comprehensive systematic review and meta-analysis, which specifically assesses the effects of ginseng on blood lipids. Here we, therefore, aimed to perform a systematic review and meta-analysis of studies evaluating the effects of ginseng on lipid profile in adults.

## 2. Method

The current systematic review and meta-analysis was designed and reported based on the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).<sup>32</sup>

### 2.1. Search strategy

Relevant articles from the earliest available online indexing year to April 2019 were identified through searches of the literature in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>), Scopus (<http://www.scopus.com>), ISI Web of Science (<http://www.webofscience.com>), Cochrane library (<http://www.cochranelibrary.com>) and Google Scholar (<https://scholar.google.com>), without language or any other restriction. The following terms or keywords were used: ("Panax ginseng" OR

"ginseng" OR "Panax") AND ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment"). Moreover, we reviewed the reference lists from the retrieved publications and review articles to search for additional relevant studies.

### 2.2. Study selection

After conducting literature search by one investigator (E.Gh), all identified articles were exported into EndNote (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA) to eliminate duplications. Then, two authors (E.Gh and A.Gh) independently reviewed titles and abstracts of the articles to ascertain whether these studies were eligible for our meta-analysis based on inclusion criteria. The full text of all relevant records was then reviewed. Inclusion criteria were: RCTs (either parallel or crossover design); (i) investigating the impact of ginseng on plasma/serum concentrations of lipids; and (ii) with suitable controlled design, i.e., the only difference between the control and treatment groups was ginseng. Studies that administrated ginseng in combination with other components and trials without sufficient data were excluded. In the case of multiple publications from the same trial, we selected only the most recent or informative one. Any disagreements were solved through consultation with a third author (A.H).

### 2.3. Data extraction

The data extraction was performed by two independent authors (E.Gh and A.Gh) and the possible discrepancies were resolved by consensus. The extracted information was as follows: (i) study characteristics (first author's last name, year of publication, location of the study, sample size and study design); (ii) participants' information (gender, mean age, mean body mass index [BMI], and health status); (iii) intervention details (duration of treatment and ginseng dose); and (iv) investigated outcomes including total cholesterol (TC), triglyceride (TG), LDL-C, and HDL-C. We contacted the corresponding authors via e-

**Table 1**  
Characteristics of eligible studies.

First author (location; year)	RCT design (blinding)	Population	sex	Mean Age (year)	Mean BMI (kg/m <sup>2</sup> )	Sample size (Ginseng/Placebo)	Duration (Weeks)	Outcomes	Dose of Ginseng (g/day)
Vaksun (Canada; 2018)	Cross Over	T2DM	Both	64	27.8	24/24	8	TC, LDL-c, HDL-c	3
Beak (Korea; 2018)	Parallel (double)	Individuals exposed to high stress levels	Both	40.42	22.73	32/31	6	TC,TG,LDL-c, HDL-c	0.5
Hwang (a) (Korea; 2018)	Parallel (double)	Healthy(GS-3K8)	Both	52	ND	14/15	12	TC, TG	ND
Hwang (b) (Korea; 2018)	Parallel (double)	Healthy (GiNST)	Both	52	ND	15/15	12	TC, TG	ND
Choi (Korea; 2017)	Parallel (double)	Healthy	Both	52.32	25.56	29/34	12	TC,TG,LDL-c, HDL-c	1
Jong (Korea; 2016)	Parallel (double)	Metabolic syndrome	Men	46.7	28.8	32/30	4	TC,TG, HDL-c	3
Park (Korea; 2016)	Parallel (double)	Healthy	Both	51.15	ND	39/39	24	TC,TG,LDL-c, HDL-c	0.75
Hong (Korea; 2015)	Parallel (double)	NAFLD	Both	47.8	27.9	35/31	3	TC	1.35
Bang (Korea; 2014)	Parallel (double)	Newly Diagnosed Type 2 Diabetes Mellitus	Both	57.45	23.66	21/20	12	TC,TG,LDL-c, HDL-c	5
Raoh (Korea; 2014)	Parallel (double)	T2DM	Both	53.35	24.9	21/21	4	TC,TG,LDL-c, HDL-c	2.7
Cho (Korea; 2013)	Parallel (double)	Overweight and obese adults	Both	42.85	26.2	34/34	12	TC,TG,LDL-c, HDL-c	6
Hassanzadeh (Iran; 2013)	Parallel (double)	Hyperlipidemic	Both	28.45	ND	18/18	8	TC,TG,LDL-c, HDL-c	0.5
Hosseini (Iran; 2013)	Parallel (double)	T2DM	Both	47.05	30.25	15/15	8	TC,TG,LDL-c, HDL-c	0.3
Kwon (Korea; 2012)	Parallel (double)	Obese	Women	43.69	28.80	22/23	8	TC,TG, HDL-c	6
Park (Korea; 2012)	Parallel (double)	Metabolic syndrome	Both	44.65	ND	23/25	12	TC,TG, HDL-c	4.5
Lee(a) (Korea; 2012)	Parallel (double)	Healthy Volunteers	Men	40.30	22.6	56/57	4	TC,TG,HDL-c	0.5
Lee(b) (Korea; 2012)	Parallel (double)	Healthy Volunteers	Men	40.30	22.6	57/57	4	TC,TG,HDL-c	1
Lee © (Korea; 2012)	Parallel (double)	Healthy Volunteers	Women	41.05	22.45	56/57	4	TC,TG,HDL-c	0.5
Lee (d) (Korea; 2012)	Parallel (double)	Healthy Volunteers	Women	41.05	22.45	57/57	4	TC,TG,HDL-c	1
Kim (Korea; 2011)	Parallel (double)	T2DM	Both	53.74	24.36	20/18	12	TC,TG,LDL-c, HDL-c	0.78
Kim (Korea; 2011)	Parallel (double)	Postmenopausal	Women	54.04	22.19	36/36	12	TC,TG,LDL-c, HDL-c	3
Shin (Korea; 2011)	Parallel (double)	Impaired fasting glucose	Both	44.4	25.15	15/15	8	TC, LDL-c, HDL-c	20
Yoon (a) (Korea;2011)	Parallel (double)	T2DM	Both	53.75	25.8	18/18	8	TC,TG,LDL-c, HDL-c	1.5
Yoon (b) (Korea;2011)	Parallel (double)	T2DM	Both	53.75	24.65	18/18	8	TC,TG,LDL-c, HDL-c	2
Yoon (c) (Korea;2011)	Parallel (double)	T2DM	Both	52.95	25.35	18/18	8	TC,TG,LDL-c, HDL-c	3
Reeds (USA; 2011)	Parallel (double)	Impaired glucous tolerance	Both	46	33	5/5	4	TC,TG,LDL-c, HDL-c	8
Rhee (Korea; 2010)	Parallel (double)	Hypertension	Both	56.5	24.8	30/34	12	TC,TG,LDL-c, HDL-c	3
Chung (Korea; 2010)	Cross Over	Coronary Artery Disease	Both	62.4	25.5	20/20	10	TC	2.7
Ahn (Korea; 2010)	Parallel (double)	AMI	Both	60.45	24.45	25/25	32	TC,TG,LDL-c, HDL-c	3
Shin (a) (Korea; 2007)	Parallel (double)	Healthy	Both	40	ND	29/29	?	TC,TG,LDL-c, HDL-c	ND (Low dose)
Shin (b) (Korea; 2007)	Parallel (double)	Healthy	Both	40	ND	29/29	?	TC,TG,LDL-c, HDL-c	ND (High dose)
Andrade (Brazile; 2007)	Parallel (double)	Erectile dysfunction	Men	53.45	ND	30/30	12	TC,LDL-c, HDL-c	1
Soo kim (a) (Korea; 2002)	Parallel (ND)	Healthy	Women	20.57	ND	7/7	12	TC,TG,LDL-c, HDL-c	?
Soo kim (b) (Korea; 2002)	Parallel (ND)	Healthy	Women	21.14	ND	7/7	12	TC,TG,LDL-c, HDL-c	?
Kim (Korea; 2001)	Parallel (double)	Smoker	Men	23	ND	15/5	4	TC,TG,LDL-c, HDL-c	1.8

AMI; acute myocardial infarction; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; HC, hip circumference; ND, non-defined.

**Table 2**  
Risk of bias assessment for included randomized controlled clinical trials.

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Vuskan (2018)	L	L	L	L	L	L
Beak (2018)	L	L	L	L	H	L
Hwang (2018)	L	L	L	L	L	L
Choi (2017)	U	L	L	L	L	L
Jung (2016)	L	L	L	U	L	U
Park (2016)	L	L	L	H	L	L
Hong (2015)	L	L	U	U	U	L
Bang (2014)	U	U	L	U	L	U
Raoh (2014)	L	L	L	L	L	U
Cho (2013)	U	U	L	U	L	U
Hassanzadeh (2013)	U	U	L	U	L	U
Hosseini (2013)	U	L	L	L	L	U
Kwon (2012)	L	L	L	L	L	L
Park (2012)	L	U	L	U	L	U
Lee (2012)	L	L	U	U	L	U
Kim (2011)	U	U	L	U	L	U
Shin (2011)	U	U	U	U	L	U
Yoon (2011)	L	L	U	U	L	L
Reeds (2011)	L	L	L	L	L	L
Rhee (2010)	U	L	U	U	L	L
Chung (2010)	U	U	U	U	L	L
Ahn (2010)	U	U	H	H	L	L
Shin (2007)	U	U	U	U	U	L
Andrade (2007)	L	U	U	U	L	L
So kim (2002)	U	U	H	U	L	L
Kim (2001)	U	U	U	U	L	U
Kim (2011)	L	L	L	U	U	U

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

mail in case further information was required.

#### 2.4. Quality assessment

We assessed the methodological quality of each included trial by using the Cochrane Collaboration's tool, which assigns scores for following domains: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "low risk of bias", "high risk of bias" or "unclear risk of bias" was made in each domain. Finally, the overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item), and weak (low risk for less than 2 item).<sup>33</sup> The quality assessment was conducted by E.Gh and A.Gh independently and was discussed with A.H in case of inconsistencies.

#### 2.5. Statistical analysis

Statistical analyses were carried out using the STATA software (version 11.0; Stata Corporation). All data were collected as means  $\pm$  standard deviation (SD) for each variable in similar unit (mg/dl) to estimate the pooled effects. In studies in which mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. Also, the SD of mean change was calculated as follows:  $[SD = \text{square root } [(SD \text{ pre-treatment})^2 + (SD \text{ post-treatment})^2 - (2R \times SD \text{ pre-treatment} \times SD \text{ post-treatment})]]$ , assuming a correlation coefficient of 0.5. To make sure that our meta-analysis is not sensitive to the selected correlation coefficient, all the analyses for each parameter was repeated by the use of correlation coefficient of 0.2 and 0.8. When standard error (SE) was reported in place of SD, we converted it to SD for further analyses:  $SD = SE \times \sqrt{n}$ ;  $n$  = number of subjects. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated

for net changes by using the random-effects model which takes the between-study heterogeneity into account. Heterogeneity among studies was assessed by the  $p$  value and  $I^2$  statistic. Substantial heterogeneity exists when  $I^2$  exceeds 50% or  $p$  value was less than 0.05.<sup>34</sup> To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on gender (male, female, or both), intervention duration ( $\geq 12$  or  $< 12$  weeks), ginseng dose ( $< 1500$  or  $\leq 1500$  mg/day), and type of study population (healthy or unhealthy). Heterogeneity between subgroups was evaluated using fixed-effect model. To determine if any single clinical trial with extreme findings had an undue influence on the overall results, sensitivity analysis was performed. We estimated publication bias with visual inspection of funnel plots and Begg's rank-correlation method. In addition, the trim-and-fill approach was performed to obtain an adjusted effect size that takes into account publication bias. All tests were two-tailed and  $p < 0.05$  indicated statistical significance.

### 3. Result

#### 3.1. Study selection

Our search identified 1245 articles through databases searching (Fig. 1). After removing duplicate publications ( $n = 210$ ), 1035 articles remained for screening the titles or abstracts. Of them 1001 records were excluded due to irrelevance to the inclusion criteria and duplication. Among 34 remaining articles, 7 records were excluded due to the following reasons: 1) without sufficient data ( $n = 2$ ), 2) without a placebo group ( $n = 1$ ), and 3) used mixture of ginseng with other compounds ( $n = 4$ ). Finally, 27 articles,<sup>10,11,17,20,27,29–31,35–53</sup> with 35 arms were included in the present systematic review and meta-analysis.

#### 3.2. Study characteristics

Included studies have been published between 2001 and 2018. A total of 1839 subjects (922 cases and 917 controls) were included in analysis. Twenty five studies had parallel design while two studies had

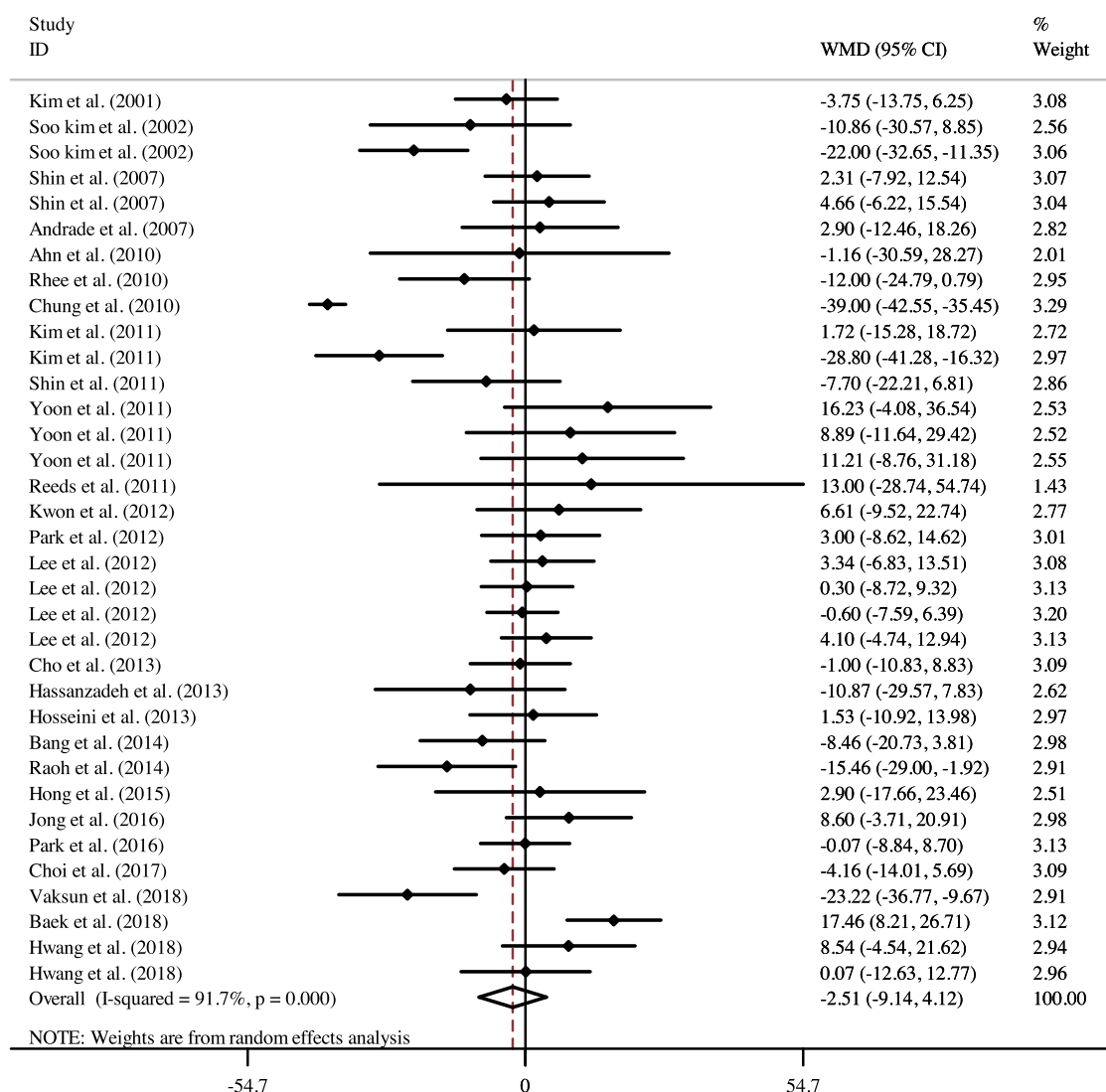


Fig. 2. Forest plot of the effect of ginseng supplementation on total cholesterol.

cross-over design.<sup>30,39</sup> Out of 27 included studies, 22 studies performed in South Korea,<sup>10,11,17,20,29,35–39,41–43,45–54</sup> 2 trials in Iran,<sup>27,31</sup> 1 trial in Canada,<sup>30</sup> 1 trial in USA<sup>17</sup> and 1 trial in Brazil.<sup>40</sup> The intervention period ranged between 3 and 32 weeks. Supplementation dose of ginseng ranged from 0.5 g to 20 g. Twenty-one of included studies were conducted on both genders, 3 trials were conducted on men<sup>40,43,45</sup> and 3 trials were conducted on women.<sup>29,46,47</sup> Included studies were carried-out in subjects with type 2 diabetes,<sup>20,27,30,36,44,53</sup> impaired fasting glucose,<sup>17,52</sup> healthy subjects,<sup>10,38,42,46,48,51</sup> individuals exposed to high stress levels,<sup>11</sup> non-alcoholic fatty liver,<sup>41</sup> hyperlipidemic,<sup>31</sup> post-menopausal,<sup>29</sup> hypertension,<sup>50</sup> coronary artery disease,<sup>39</sup> acute myocardial infarction,<sup>35</sup> erectile dysfunction,<sup>40</sup> overweight and obese subjects,<sup>37,47</sup> and metabolic syndrome.<sup>43, 49</sup> Detailed characteristics of included trial are present in Table 1.

### 3.3. Risk of bias assessment

Random allocation and method of random sequence generation of participants was mentioned in 14 trials<sup>10,11,17,20,29,30,40–43,47–49,53</sup> although that was not clear in 13 trials.<sup>27,31,35–39,44–46,50–52</sup> Fifteen trials reported allocation concealment.<sup>10,11,15,17,20,27,30,38,41–44,47,50,53,55</sup> Most of the included studies had low/unclear risk of bias in blinding of participants, personnel and outcome assessors, except Park et al.,<sup>49</sup> Ahn et al.<sup>35</sup> and So kim et al.<sup>46</sup> studies. Most studies showed low/unclear

risk of bias based on incomplete outcome data and selective outcome reporting exception Beak et al. study.<sup>11</sup> Details of risk of bias assessment are presented in Table 2.

### 3.4. Finding from meta-analysis

#### 3.4.1. Effect of ginseng supplementation on TC

Among included studies, thirty-five trials reported the effect of ginseng supplementation on TC which included a total of 1839 participants (922 interventions, and 917 control group). Pooled effect size showed that TC did not change following ginseng supplementation (WMD: -2.512 mg/dl, 95% CI: -9.143, 4.118;  $p = 0.458$ ) with significant between study heterogeneity ( $I^2 = 91.7\%$ ,  $p < 0.001$ ) (Fig. 2).

Subgroup analysis were performed based on gender (male/female/both), dose ( $\leq 1500$  mg/  $> 1500$  mg), intervention duration ( $< 12$  weeks/ $\geq 12$  weeks) and study population (healthy/unhealthy). Subgroup analysis revealed that higher doses (more than 1500 mg/day of ginseng) and longer duration ( $\geq 12$  weeks) showed significant lowering effect of ginseng. Furthermore, ginseng supplementation showed significant TC lowering effect in unhealthy subjects. However, there were no significant effect for low dose supplementation, short duration and in healthy and male subjects.

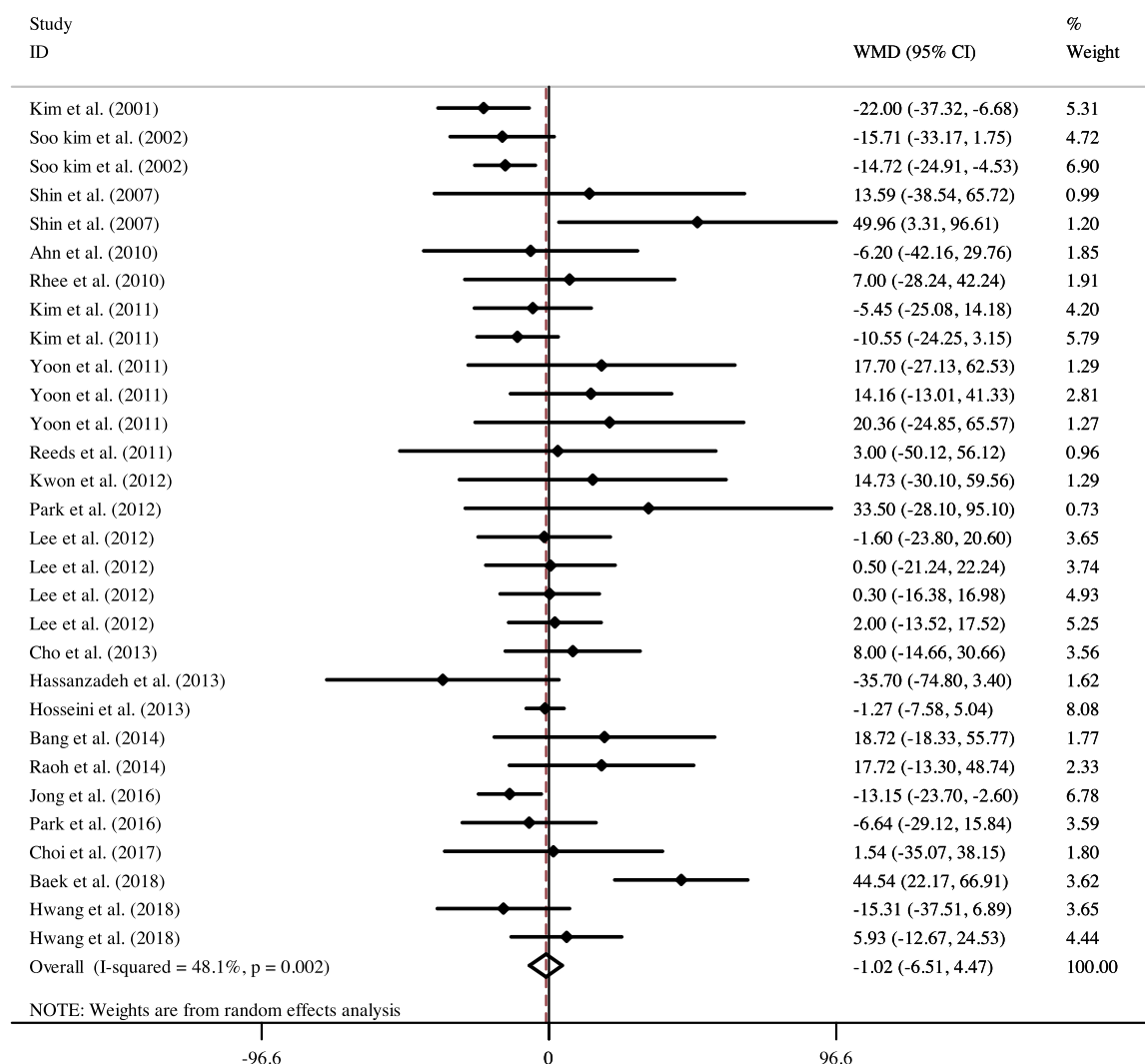


Fig. 3. Forest plot of the effect ginseng supplementation on triglyceride.

### 3.4.2. Effect of ginseng supplementation on TG

A total of thirty studies reported triglyceride as an outcome measure following ginseng supplementation. It covers 1594 participants (798 interventions, and 796 control group). Pooled analysis revealed no significant effect following ginseng supplementation (WMD:  $-1.022$  mg/dl, 95% CI:  $-6.513$ ,  $4.468$ ,  $p = 0.715$ ) with significant across-study heterogeneity ( $I^2 = 80.4\%$ ,  $p < 0.001$ ) (Fig. 3).

Subgroup analysis revealed significant lowering effect in high doses, longer duration and only in healthy subjects; this effect remained non-significant in lower doses and unhealthy subjects, as outlined in Table 3.

### 3.4.3. Effect of ginseng supplementation on LDL-C

Across included datasets, twenty-four RCTs reported results for LDL-C covering 1065 participants (535 interventions, and 530 control group). Combined results showed no significant effect on LDL-C following ginseng supplementation (WMD:  $-3.282$  mg/dl, 95% CI:  $-8.311$ ,  $1.747$ ,  $p = 0.201$ ). However, there was significant heterogeneity across the included RCTs ( $I^2 = 77.4\%$ ,  $p < 0.001$ ) (Fig. 4).

Subgroup analysis showed that high doses of ginseng supplementation showed significant lowering effect; effect was significant in healthy subjects and in both duration ( $< 12$  weeks/ $\geq 12$  weeks).

### 3.4.4. Effect of ginseng supplementation on HDL-C

Of all 35 included trials, thirty-one studies reported the effect of

ginseng supplementation on HDL-C level which included 1673 participants (838 interventions, and 835 control group). We found that ginseng supplementation did not affect HDL-C significantly (WMD:  $0.809$  mg/dl, 95% CI:  $-0.734$ ,  $2.352$ ,  $p = 0.304$ ) (Fig. 5). We found significant heterogeneity across studies ( $I^2 = 80.4\%$ ,  $p < 0.001$ ).

Subgroup analysis showed that HDL-cholesterol increased significantly in low doses of ginseng supplementation and in healthy subjects but in both duration ( $< 12$  weeks/ $\geq 12$  weeks).

### 3.4.5. Publication bias and Trim and Fill sensitivity analysis

Assessment of publication bias by visual inspection of funnel plot and Begg's test performed for possible publication bias. There was no publication bias for LDL-C ( $p = 0.519$ ). However, Begg's test showed significant publication bias for TG ( $p = 0.016$ ). Funnel plots for HDL-C and TC also showed significant publication bias among included studies. Because of significant publication bias tests, we performed the trim and fill sensitivity analysis. The trim and fill analysis was calculated from 31 hypothesized negative unpublished studies for HDL-C. The corrected effect size of "publication bias" unchanged; trim and fill analysis were statistically significant as well ( $p < 0.001$ ). Therefore, results could not be changed if other new studies publish regarding HDL-C. However, the trim and fill analysis for TG from 39 unpublished negative studies reclined to  $-6.143$  mg/dl (95% CI:  $-12.165$ ,  $-0.122$ ), the new pooled effect size were significant ( $p = 0.046$ ). The trim and fill analysis for TG also were significant ( $p < 0.001$ ). The trim



**Table 3**  
Subgroup analysis to assess the effect of ginseng supplementation on lipid profile.

Subgrouped by	No. of trials	WMD (95% CI)	P Value	P for heterogeneity	I <sup>2</sup> (%)	P for between subgroup heterogeneity
Total Cholesterol						
Total	35	<b>-2.512 -9.143 4.118</b>	<b>0.458</b>	<b>0.000</b>	<b>91.7</b>	
Gender						0.000
Male	5	1.577 -3.257 6.411	0.523	0.634	0	
Female	6	-6.212 -10.480 -1.944	0.004	0.000	84.1	
Both	24	-14.446 -16.604 -12.288	0.000	0.000	93.2	
Dosage						0.000
≤ 1500 mg	13	2.497 -0.490 5.485	0.101	0.148	29.5	
> 1500 mg	16	-22.299 -24.807 -19.791	0.000	0.000	92.8	
Intervention Duration (Weeks)						0.000
< 12 weeks	18	1.299 -1.557 4.156	0.373	0.001	58.3	
≥ 12 weeks	15	-20.922 -23.334 -18.510	0.000	0.000	93.7	
Type of Study Population						0.000
Healthy	18	-0.411 -2.862 2.039	0.742	0.000	70.4	
Unhealthy	17	-22.661 -25.278 -20.043	0.000	0.000	92.3	
Low Density Lipoprotein						
Total	24	<b>-3.282 -8.311 1.747</b>	<b>0.201</b>	<b>0.000</b>	<b>77.4</b>	
Gender						0.000
Male	2	-16.307 -20.863 -11.751	0.000	0.010	84.8	
Female	3	-18.055 -24.297 -11.814	0.000	0.410	0	
Both	19	0.095 -2.718 2.908	0.947	0.001	56.6	
Dosage						0.000
≤ 1500 mg	8	3.128 -0.938 7.195	0.132	0.073	45.9	
> 1500 mg	12	-11.091 -14.068 -8.115	0.000	0.000	74.4	
Intervention Duration (Weeks)						0.036
< 12 weeks	11	-5.852 -9.033 -2.671	0.000	0.000	86.1	
≥ 12 weeks	11	-8.280 -11.703 -4.856	0.000	0.010	56.8	
Type of Study Population						0.014
Healthy	11	-8.059 -10.754 -5.364	0.000	0.000	85.3	
Unhealthy	13	-2.039 -6.038 1.960	0.318	0.006	56.9	
High Density Lipoprotein						
Total	31	<b>0.809 -0.734 2.352</b>	<b>0.304</b>	<b>0.000</b>	<b>80.4</b>	
Gender						0.000
Male	5	4.860 3.602 6.117	0.000	0.000	95	
Female	6	1.604 0.362 2.845	0.011	0.064	52.1	
Both	20	-0.776 -1.760 0.208	0.122	0.760	0	
Dosage						0.005
≤ 1500 mg	12	2.494 1.564 3.425	0.000	0.000	88.6	
> 1500 mg	15	0.082 -1.078 1.241	0.890	0.019	48.3	
Intervention Duration (Weeks)						0.000
< 12 weeks	17	1.217 0.327 2.107	0.007	0.031	42.9	
≥ 12 weeks	12	2.620 1.553 3.688	0.000	0.000	89.7	
Type of Study Population						0.001
Healthy	16	2.172 1.377 2.967	0.000	0.000	88.9	
Unhealthy	15	-0.169 -1.337 0.999	0.777	0.905	0	
Triglyceride						
Total	30	<b>-1.022 -6.513 4.468</b>	<b>0.715</b>	<b>0.002</b>	<b>48.1</b>	
Gender						0.001
Male	4	-12.311 -19.896 -4.726	0.001	0.285	20.8	
Female	6	-8.789 -14.934 -2.644	0.005	0.304	17	
Both	20	2.506 -2.103 7.114	0.287	0.035	39.7	
Dosage						0.041
≤ 1500 mg	11	0.520 -4.169 5.209	0.828	0.031	49.7	
> 1500 mg	13	-6.457 -12.564 -0.351	0.038	0.109	34.2	
Intervention Duration (Weeks)						0.028
< 12 weeks	15	-1.857 -6.040 2.327	0.384	0.001	61.0	
≥ 12 weeks	13	-7.596 -13.102 -2.091	0.007	0.461	0	
Type of Study Population						0.507
Healthy	17	-4.694 -9.292 -0.096	0.045	0.001	60.7	
Unhealthy	13	-2.445 -7.231 2.342	0.317	0.259	18.3	

and fill sensitivity method was calculated from 51 hypothesized negative unpublished studies for TC. The corrected effect size of “publication bias” changed to -15.106 mg/dl (95 % CI: -21.314, -8.899), which was significant ( $p < 0.001$ ). The sensitivity analysis was significant ( $p < 0.001$ ). It showed the significant effect of publication bias on overall estimate of effect size.

#### 3.4.6. Sensitivity analysis

Sensitivity analysis indicated that no study had significant impact on the overall effect sizes of TC, LDL-C and HDL-C. However the results of sensitivity analysis showed that removing the study by Baek et al.<sup>11</sup>

changed the overall effect of ginseng supplementation on TG level (WMD: -3.91 mg/dl, 95 CI%: -8.43, 0.615) but remained statistically non-significant.

#### 4. Discussion

Findings from our meta-analysis did not support the beneficial effect of ginseng supplementation on blood TC, TG, LDL-C, and HDL-C levels. However, in subgroup analyses, results were changed significantly based on study population, supplement dose and duration of treatment.

To the author's knowledge, one additional systematic review and

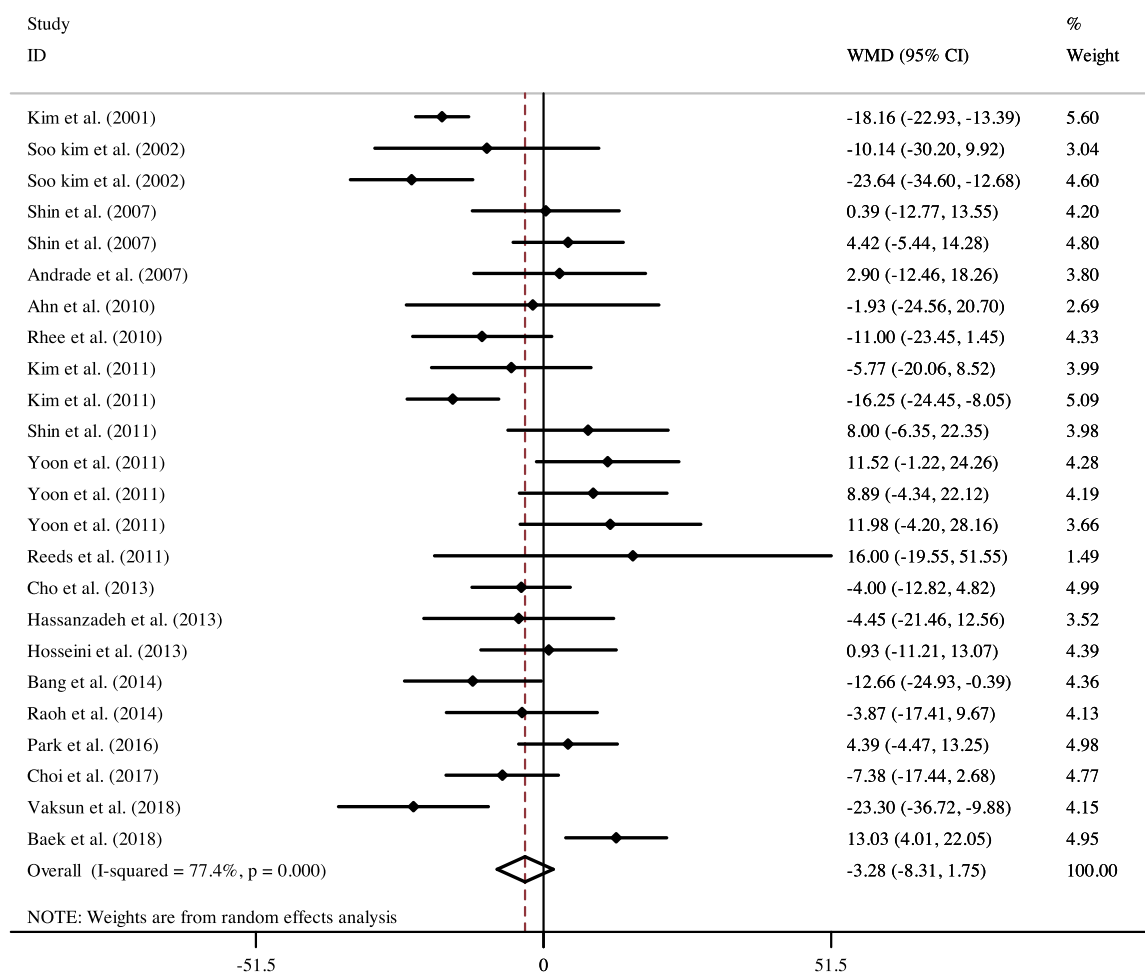


Fig. 4. Forest plot of the effect of ginseng supplementation on LDL- cholesterol.

meta-analysis has been done in this area, but not specifically studying the effect of ginseng on lipid profile.<sup>56</sup> Gui et al.<sup>56</sup> reported an improved lipid profile (TG, total cholesterol, and LDL-C but not HDL-C) associated with ginseng-related therapy in patients with type-2 diabetes (T2DM) or impaired glucose tolerance. Due to the limited number of RCTs included (five RCTs) and therefore insufficient sample size, results of mentioned meta-analysis must be interpreted with caution. Furthermore, study population in this study was limited only to those with prediabetes or T2DM. Given that, RCTs included in our meta-analysis were with different study populations, our findings seem more reliable.

Evidence from pre-clinical studies are inconsistent, however, many support the beneficial effects of ginseng on lipid profile.<sup>22,24–26,55,57,58</sup> Administration of ginseng saponins have been associated with lipoprotein lipase activation in hyperlipidemic rabbits.<sup>22</sup> Further, positive effects of ginseng are mainly observed in vitro, or when intraperitoneal injection is used; however, it should be considered that the lipid metabolism in rats and mice is different from humans.<sup>59</sup> Mechanistically, ginsenosides are purportedly able to increase the accumulation of triglyceride in adipose tissue as a result of its stimulating action on the lipogenic pathway and lipoprotein lipase,<sup>55</sup> and also promote the synthesis of LDL-C receptors in rats.<sup>60</sup> Therefore, the evidence from animal studies should be verified in clinical trials.

In the present study we found no significant effect of ginseng supplementation on lipid profile. The discrepancies between included studies could be explained by several possible reasons: 1) different sample size; 2) Intervention period: most of included studies were less than 12 weeks, however, shorter clinical studies suggested that health benefits of antioxidant therapy were observed after at least 12–17

months<sup>61</sup>; 3) Dose and form of ginseng used: although most of included trials provided ginseng, the composition of the supplement were different, where few of included studies provided specific details regarding the standardization of formula. Moreover, ginseng products used in include studies varied substantially (American ginseng, Korean red ginseng, *Panax* ginseng extract, fermented red ginseng, Ginsam, enzyme treated red ginseng and protopanaxadiol-enriched ginseng extract). Factors regarding the study design should be considered, including the dosage and duration of intervention and participant characteristics. Similarly, studies included were significantly different, in terms of the dose (0.3–8 g/day) and duration of treatment (3–32 weeks). Since no dose-escalation study has been conducted to elucidate optimal dosage, it is unclear whether the administrated dose in the trials was adequate to elicit a substantial, anti-hyperlipidemic effect in a clinical setting. 4) Human body metabolism: discrepancy between pre-clinical data and our results may be explained by limited systemic bioavailability of ginseng metabolites after oral administration, which can limit their efficacy in humans.<sup>17</sup> In addition, ginsenosides are transformed substantially by intestinal flora after oral ingestion.<sup>39</sup> Thus, the composition and distribution of gut microbiota are likely influential, and, indeed, warrant further investigation.

The most bioactive compounds in ginseng are ginseng-specific saponins or ginsenosides, which are comprised of a steroid skeleton and sugar molecules. The type, number and position of the sugars determine their structure and function. Different ages and species of ginseng, as well as, various processing or extraction methods and part of the plant (root, leaf or berry), lead to variability in ginsenoside composition of a product and finally the antihyperlipidemic efficacy of that product.<sup>53, 62</sup>



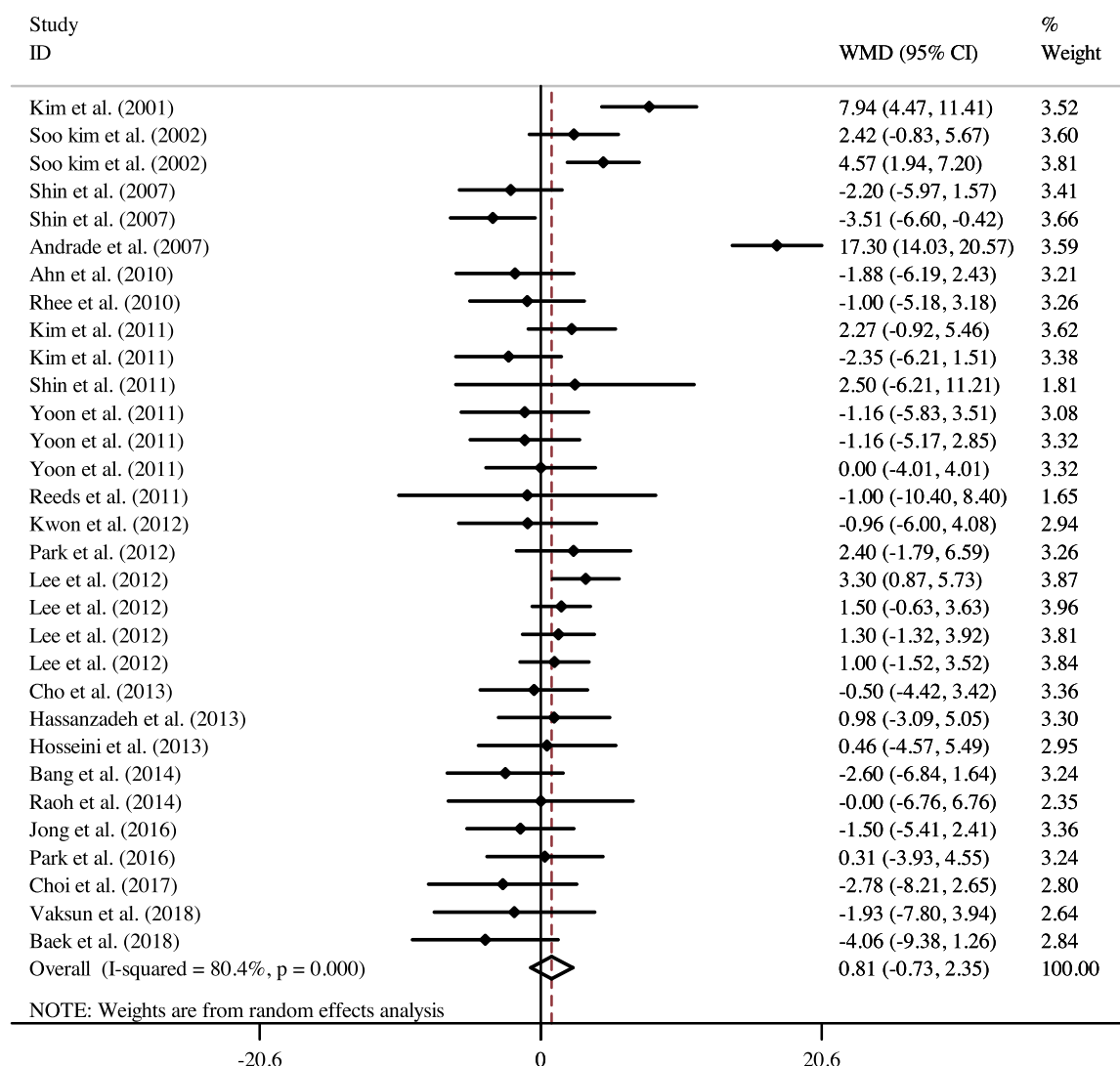


Fig. 5. Forest plot of the effect of ginseng supplementation on HDL- cholesterol.

In this case, protopanaxodial-to-protopanaxotrial ratio (PPD:PPT) has been proposed to be influential.<sup>63</sup> The discrepancy between the findings from studies investigating the antihyperlipidemic properties of ginseng on humans could be attributed partly to these differences.

In the present study, we observed significant evidence of between study heterogeneity in most cases. Subgroup analysis revealed that supplement dosage, duration of intervention and health status of participants significantly affect the impact of ginseng on blood lipids. The lowering effect of ginseng supplementation on TC, LDL-C and TG was significant with higher doses ( $\geq 1500$  mg/day) of treatment. Based on the overall findings of a meta-analysis on 26 statin trials, that every 38.7 mg/dl of reduction in serum LDL-C, induced a 22% decrease in major vascular events,<sup>64</sup> the abovementioned reduction in serum LDL-C level, would be of a great benefit, regarding clinical outcomes. Furthermore, a 23.16 mg/dl difference in TC level, has been reported to cause a 27% relative difference in coronary risk.<sup>65</sup> Additionally, the impact of ginseng on TC and TG was significant in studies with longer duration of intervention ( $\geq 12$  weeks). In this case, we found a -7.59 mg/dl reduction in serum TG concentrations, in long-term trials. Based on epidemiological evidence, increased TG or triglyceride-rich lipoproteins can be considered as an additional cause of cardiovascular disease and all-cause mortality.<sup>66</sup>

Several mechanisms have been proposed to explain the beneficial effects of ginseng on blood lipids, including anti-inflammatory and anti-

oxidative properties of ginseng, regulating lipoprotein metabolism through alteration of PPAR $\gamma$  expression and reducing hepatic cholesterol and TG levels by activation of AMP-activated protein kinase (AMPK) and inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) expression.<sup>23,27,28</sup> The lack of any significant effect in some studies has been attributed to short duration of treatment or lower dosage of ginseng.<sup>20,27,31,50</sup> Interestingly, HDL-C has reportedly been increased in studies using low doses of ginseng, however, we could not delineate any reason for this finding, and represents an area of interest for future research.

The present meta-analysis has several limitations which should be considered when interpreting the results. First, studies included were highly varied in terms of type and dosage of ginseng products used, which might lead to different results, whilst the lack of standardization of ginseng formulas presents issues. Second, follow-up duration and sample sizes were not sufficient in several included trials. Third, most studies did not adjust their results for confounding variables; there are several parameters which must be considered in this context, including diet,<sup>67–69</sup> weight<sup>70</sup> and exercise.<sup>71</sup> Finally, significant heterogeneity was observed for all blood lipids, which was not explained by subgroup analyses completely. This meta-analysis also has several strengths. First, we conducted a comprehensive search to find all relevant published articles. In addition, all studies included were RCTs, which provide the most reliable, causal results, in comparison with observational studies.

## 5. Conclusion

In conclusion, the results from present systematic review and meta-analysis did not support the beneficial effects of ginseng supplementation on blood lipids, including TC, TG, LDL-C, and HDL-C. However, subgroup analyses showed a significant lowering effect in high dose ginseng supplementation on TC, LDL-C and TG. Also, the impact of ginseng on TC and TG is significant in long-term interventions. Finally, well-designed, longer duration clinical trials with standardized formulas are needed to elucidate the effectiveness of ginseng more conclusively.

## Declaration of competing interest

The authors declare no conflict of interest.

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## References

- Zhan J, Liu Y-J, Cai L-B, et al. Fruit and vegetable consumption and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr*. 2017;57(8):1650–1663.
- Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, et al. White rice consumption and CVD risk factors among Iranian population. *J Health Popul Nutr*. 2013;31(2):252–261.
- Jolfaie N, Rouhani M, Surkan P, Siassi F, Azadbakht LJH, Research M. Rice bran oil decreases total and LDL cholesterol in humans: a systematic review and meta-analysis of randomized controlled clinical trials. *Horm Metab Res*. 2016;48(07):417–426.
- Cifková R, Krajčoviechová AJC. Dyslipidemia and cardiovascular disease in women. *Curr Cardiol Rep*. 2015;17(7):52.
- Liu C, Sun J, Lu Y, YJ Po Bo. Effects of anthocyanin on serum lipids in dyslipidemia patients: a systematic review and meta-analysis. *PLoS One*. 2016;11(9):e0162089.
- Rouhani MH, Rashidi-Pourfard N, Salehi-Abargouei A, Karimi M, Haghighatdoost F. Effects of egg consumption on blood lipids: a systematic review and meta-analysis of randomized clinical trials. *J Am Coll Nutr*. 2018;37(2):99–110.
- Sahebkar A, Serban M-C, Gluba-Brzozka A, et al. Lipid-modifying effects of nutraceuticals: an evidence-based approach. *Nutrition*. 2016;32(11–12):1179–1192.
- Cicero AFG, Colletti A, Bajraktari G, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr Rev*. 2017;75(9):731–767.
- Yun T-K. Experimental and epidemiological evidence on non-organ specific cancer preventive effect of Korean ginseng and identification of active compounds. *Mutat Res*. 2003;523–524:63–74.
- Park S-Y, Shin Y-K, Kim H-T, et al. A single-center, randomized, double-blind, placebo-controlled study on the efficacy and safety of “enzyme-treated red ginseng powder complex (BG11001)” for antiwrinkle and proelasticity in individuals with healthy skin. *J Ginseng Res*. 2016;40(3):260–268.
- Baek JH, Heo J-Y, Fava M, et al. Effect of Korean red ginseng in individuals exposed to high stress levels: a 6-week, double-blind, randomized, placebo-controlled trial. *J Ginseng Res*. 2018;43(3):402–407.
- Hong C-E, S-YJ In Lyu. Anti-inflammatory and anti-oxidative effects of Korean red ginseng extract in human keratinocytes. *Immune Netw*. 2011;11(1):42–49.
- Qi L-W, Wang C-Z, Yuan C-S. Ginsenosides from American ginseng: chemical and pharmacological diversity. *Phytochemistry*. 2011;72(8):689–699.
- Coon JT, Ernst E. Panax ginseng. *Drug Saf*. 2002;25(5):323–344.
- Lee SM, Bae B-S, Park H-W, et al. Characterization of Korean Red Ginseng (Panax ginseng Meyer): history, preparation method, and chemical composition. *J Ginseng Res*. 2015;39(4):384–391.
- Sun S, Qi L-W, Du G-J, Mehendale SR, Wang C-Z, Yuan C-S. Red notoginseng: Higher ginsenoside content and stronger anticancer potential than Asian and American ginseng. *Food Chem*. 2011;125(4):1299–1305.
- Reeds DN, Patterson BW, Okunade A, Holloszy JO, Polonsky KS, Klein SJD. Ginseng and ginsenoside Re do not improve  $\beta$ -cell function or insulin sensitivity in overweight and obese subjects with impaired glucose tolerance or diabetes. *Diabetes Care*. 2011;34(5):1071–1076.
- X-p C, Y-p L, Y-z H, C-x L, Lan K, Jia W. Phytochemistry, metabolism, and metabolomics of Ginseng. *Chinese Herb Med*. 2015;7(2):98–108.
- Wang H-Y, Qi L-W, Wang C-Z, PJTAJom Li. Bioactivity enhancement of herbal supplements by intestinal microbiota focusing on ginsenosides. *Am J Chin Med*. 2011;39(06):1103–1115.
- Oh M-R, Park S-H, Kim S-Y, et al. Postprandial glucose-lowering effects of fermented red ginseng in subjects with impaired fasting glucose or type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *BMC Complement Altern Med*. 2014;14(1):237.
- Kwak Y-S, Kyung J-S, Kim JS, Cho JY, Rhee M-H. Anti-hyperlipidemic effects of red ginseng acidic polysaccharide from Korean red ginseng. *Biol Pharm Bull*. 2010;33(3):468–472.
- Inoue M, Wu C, Dou D, Chen Y, Ogihara YJP. Lipoprotein lipase activation by red ginseng saponins in hyperlipidemia model animals. *Phytomedicine*. 1999;6(4):257–265.
- Lee S, Lee M-S, Kim C-T, Kim I-H, YJ Joms K. Ginsenoside Rg3 reduces lipid accumulation with AMP-activated protein kinase (AMPK) activation in HepG2 cells. *Int J Mol Sci*. 2012;13(5):5729–5739.
- Yamamoto M, Uemura T, Nakamura S, Uemura M, Kumagai AJT, Ajo Cm. Serum HDL-cholesterol-increasing and fatty liver-improving actions of Panax ginseng in high cholesterol diet-fed rats with clinical effect on hyperlipidemia in man. *Am J Chin Med*. 1983;11(01n04):96–101.
- Yokozawa T, Kobayashi T, Oura H, Kawashima YJC. Bulletin p. Hyperlipemia-improving effects of ginsenoside-Rb2 in streptozotocin-diabetic rats. *Chem Pharm Bull*. 1985;33(9):3893–3898.
- Zheng X, Yan YJYT. The effect of ginsenosides of ginseng stem and leaf (GSL) on the lipid regulation and lipid peroxidation in chronic hyperlipidemic rabbits. *J Nutr Biochem*. 1991;7:110–116.
- Hosseini SA, Ehsanpour A, Asgari M, Malihi R. Evaluation of standardized ginseng extract Panax (G115\*) effect on fasting blood glucose levels, glycated hemoglobin and lipid profile in patients with diabetes type 2. *JJCDC*. 2013;2(3):26–32.
- Ni H-x, Yu N-j, Yang X-h. The study of ginsenoside on PPAR $\gamma$  expression of mononuclear macrophage in type 2 diabetes. *Mol Biol Rep*. 2010;37(6):2975–2979.
- Kim SY, Seo SK, Choi YM, et al. Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial. *Menopause*. 2012;19(4):461–466.
- Vuksan V, Xu ZZ, Jovanovski E, et al. Efficacy and safety of American ginseng (Panax quinquefolius L.) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: a double-blind, randomized, cross-over clinical trial. *Eur J Nutr*. 2018:1–9.
- Hassanzadeh Delui M, Fatehi H, Manavifar M, et al. The effects of Panax ginseng on lipid profile, pro-oxidant: antioxidant status and high-sensitivity C reactive protein levels in hyperlipidemic patients in Iran. *Int J Prev Med*. 2013;1(1):1045–1051.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annu Intern Med*. 2009;151(4):264–269.
- Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- Higgins J. *Cochrane handbook for systematic reviews of interventions*. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration; 2011 www.cochrane-handbook.org.
- Ahn CM, Hong SJ, Choi SC, Park JH, Kim JS, Lim DS. Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with first ST-segment elevation acute myocardial infarction. *Phytother Res*. 2011;25(2):239–249.
- Bang H, Kwak JH, Ahn HY, Shin DY, Lee JH. Korean red ginseng improves glucose control in subjects with impaired fasting glucose, impaired glucose tolerance, or newly diagnosed type 2 diabetes mellitus. *J Med Food*. 2014;17(1):128–134.
- Cho Y-H, Ahn SC, Lee S-Y, et al. Effect of Korean red ginseng on insulin sensitivity in non-diabetic healthy overweight and obese adults. *Asia Pac J Clin Nutr*. 2013;22(3):365.
- Choi HS, Kim S, Kim MJ, et al. Efficacy and safety of Panax ginseng berry extract on glycemic control: A 12-wk randomized, double-blind, and placebo-controlled clinical trial. *J Ginseng Res*. 2018;42(1):90–97.
- Chung I-M, Lim J-W, Pyun W-B, Kim H-Y. Korean red ginseng improves vascular stiffness in patients with coronary artery disease. *J Ginseng Res*. 2010;34(3):212–218.
- De Andrade E, De Mesquita AA, de Almeida Claro J, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. *Asian J Androl*. 2007;9(2):241–244.
- Hong M, Lee YH, Kim S, et al. Anti-inflammatory and antifatigue effect of Korean Red Ginseng in patients with nonalcoholic fatty liver disease. *J Ginseng Res*. 2016;40(3):203–210.
- Hwang J-H, Park S-H, Choi E-K, Jung S-J, Pyo MK, Chae S-W. A randomized, double-blind, placebo-controlled pilot study to assess the effects of protopanaxadiol saponin-enriched ginseng extract and pectinase-processed ginseng extract on the prevention of acute respiratory illness in healthy people. *J Ginseng Res*. 2019.
- Jung D-H, Lee Y-J, Kim C-B, Kim J-Y, Shin S-H, Park J-K. Effects of ginseng on peripheral blood mitochondrial DNA copy number and hormones in men with metabolic syndrome: A randomized clinical and pilot study. *Complement Ther Med*. 2016;24:40–46.
- Kim H-O, Park M-J, Han J-S. Effects of fermented red ginseng supplementation on blood glucose and insulin resistance in type 2 diabetic patients. *Korean J Food Nutr*. 2011;40(5):696–703.
- Kim HS, Lee BM. Protective effects of antioxidant supplementation on plasma lipid peroxidation in smokers. *J Toxicol Environ Health*. 2001;63(8):583–598.
- Kim S-S, Park H-Y, Byun Y-H, et al. The effects on the blood lipid profiles and body fat by long term administration of red ginseng product. *J Ginseng Res*. 2002;26(2):67–73.
- Kwon DH, Bose S, Song MY, et al. Efficacy of Korean red ginseng by single nucleotide polymorphism in obese women: Randomized, double-blind, placebo-controlled trial.

- J Ginseng Res.* 2012;36(2):176.
48. Lee N-H, Yoo S-R, Kim H-G, Cho J-H, Son CG. Safety and tolerability of Panax ginseng root extract: a randomized, placebo-controlled, clinical trial in healthy Korean volunteers. *J Altern Complement Med.* 2012;18(11):1061–1069.
  49. Park B-J, Lee Y-J, Lee H-R, et al. Effects of Korean red ginseng on cardiovascular risks in subjects with metabolic syndrome: a double-blind randomized controlled study. *Korean J Fam Med.* 2012;33(4):190.
  50. Rhee M-Y, Kim Y-S, Bae J-H, et al. Effect of Korean red ginseng on arterial stiffness in subjects with hypertension. *J Altern Complement Med.* 2011;17(1):45–49.
  51. Shin K-S, Lee J-J, Kim Y-I, et al. Effect of Korean red ginseng extract on blood circulation in healthy volunteers: a randomized, double-blind, placebo-controlled trial. *J Ginseng Res.* 2007;31(2):109–116.
  52. Shin S-K, Kwon J-H, Jeong Y-J, Jeon S-M, Choi J-Y, Choi M-S. Supplementation of cheonggukjang and red ginseng cheonggukjang can improve plasma lipid profile and fasting blood glucose concentration in subjects with impaired fasting glucose. *J Med Food.* 2011;14(1–2):108–113.
  53. Yoon JW, Kang SM, Vassy JL, et al. Efficacy and safety of ginsam, a vinegar extract from Panax ginseng, in type 2 diabetic patients: results of a double-blind, placebo-controlled study. *J Diabetes Investig.* 2012;3(3):309–317.
  54. Kim JH, Chang MJ, Choi HD, et al. Protective effects of Haematococcus astaxanthin on oxidative stress in healthy smokers. *J Med Food.* 2011;14(11):1469–1475.
  55. Yokozawa T, Kobayashi T, Kawai A, Oura H, Kawashima YJC. Bulletin p. Stimulation of the lipogenic pathway in ginsenoside-Rb2 treated rats. *Chem Pharm Bull.* 1984;32(11):4490–4496.
  56. Q-f Gui, Z-r Xu, K-y Xu, Y-mJM Yang. The efficacy of ginseng-related therapies in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Medicine.* 2016;95(6).
  57. Gommori K, Miyamoto F, Shibata Y, et al. Effect of ginseng saponins on cholesterol metabolism. II. Effect of ginsenosides on cholesterol synthesis by liver slice. *Chem Pharm Bull.* 1976;24(12):2985–2987.
  58. Ismail MF, Gad MZ, Hamdy MA. Study of the hypolipidemic properties of pectin, garlic and ginseng in hypercholesterolemic rabbits. *Pharmacol Res.* 1999;39(2):157–166.
  59. Mohammadi M, Ramezani-Jolfaie N, Lorzadeh E, et al. Hesperidin, a major flavonoid in orange juice, might not affect lipid profile and blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. *Phytother Res.* 2019;33(3):534–545.
  60. Yokozawa T, Kobayashi T, Kawai A, Oura H, Kawashima YJC. Bulletin p. Hyperlipemia-improving effects of ginsenoside-Rb2 in cholesterol-fed rats. *Chem Pharm Bull.* 1985;33(2):722–729.
  61. Shema-Didi L, Sela S, Ore L, et al. One year of pomegranate juice intake decreases oxidative stress, inflammation, and incidence of infections in hemodialysis patients: a randomized placebo-controlled trial. *Free Radic Biol Med.* 2012;53(2):297–304.
  62. Kitts D, Hu C. Efficacy and safety of ginseng. *Public Health Nutr.* 2000;3(4a):473–485.
  63. Sievenpiper JL, Sung M-K, Di Buono M, et al. Korean red ginseng rootlets decrease acute postprandial glycemia: results from sequential preparation-and dose-finding studies. *J Am Coll Nutr.* 2006;25(2):100–107.
  64. Gotto Jr AM. Low-density lipoprotein cholesterol and cardiovascular risk reduction: how low is low enough without causing harm? *JAMA Cardiol.* 2018;3(9):802–803.
  65. Jackson R, Lawes CMM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet.* 2005;365(9457):434–441.
  66. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* 2014;384(9943):626–635.
  67. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *Am J Clin Nutr.* 2015;102(6):1347–1356.
  68. Mente A, Dehghan M, Rangarajan S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol.* 2017;5(10):774–787.
  69. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *AHA.* 2015;4(10):e002408.
  70. Zomer E, Gurusamy K, Leach R, et al. Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. *Obes Rev.* 2016;17(10):1001–1011.
  71. Sarzynski MA, Burton J, Rankinen T, et al. The effects of exercise on the lipoprotein subclass profile: a meta-analysis of 10 interventions. *Atherosclerosis.* 2015;243(2):364–372.